SYNTHESIS OF 5-ARYLAMINO-3-ARYLIMINO-1,2-DITHIOLE-4-SULFONAMIDES FROM METHANESULFONAMIDES AND ARYL ISOTHIOCYANATES

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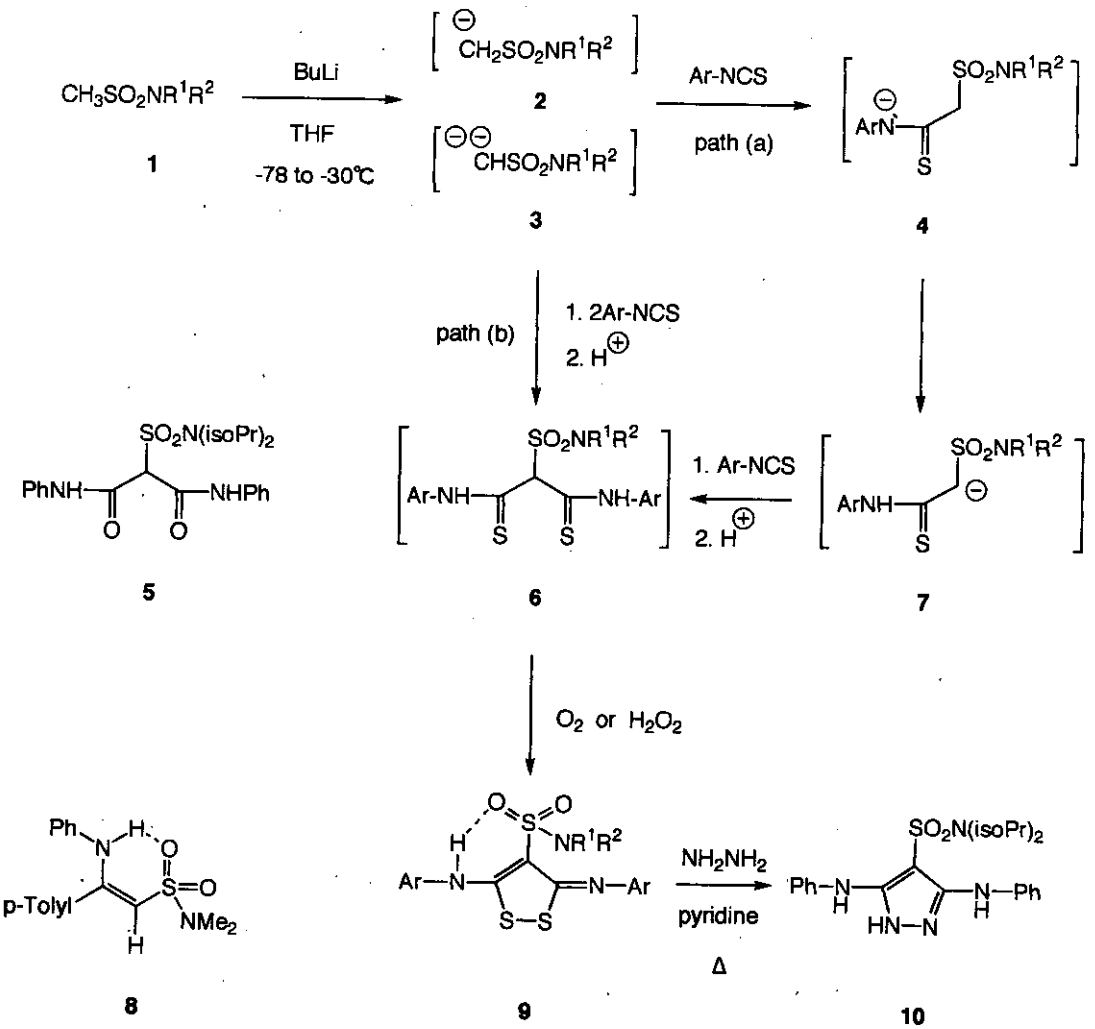
Abstract- 5-Arylamino-3-arylimino-1,2-dithiole-4-sulfonamides were obtained in one pot by the reaction of methanesulfonamides with aryl isothiocyanates in the presence of butyllithium followed by oxidation with hydrogen peroxide.

The synthetic utilities of α-carbanions, α, α-dicarbanions, and α, α'-dicarbanions of alkyl sulfones have been widely studied in recent years.[1] In contrast to alkyl sulfones, the corresponding carbanions of alkanesulfonamides have attracted less attention.[2] Active methylene compounds, for example, 2-oxo-alkanesulfonamides[3] or (ethoxycarbonyl)methanesulfonamides[4] have been used as the building blocks for heterocycles. However, the synthesis of heterocycles using simple alkanesulfonamides bearing no additional activating groups has been realized only in recent years; in 1984, Thompson reported the formation of 1,2-diazetidine 1,1-dioxides from the α,*N*-dianion of alkanesulfonamides.[5] He also reported the synthesis of 2*H*-1,2,4-thiadiazin-3-ones and 5,6-dihydro-1,4,3-oxathiazin-3-one 4,4-dioxides.[6] The latter heterocyclic ring system was also prepared from α,*N*-dianion of alkanesulfonamides and formaldehyde.[7] Furthermore, base treatment of *N*-(alkanesufonyl)amidines of α-keto acids gave the intramolecular cyclization products, 3-aminoisothiazole *S*,*S*-dioxides.[8] In the course of our studies on the synthesis of trifluoromethylated heterocycles starting from the carbanions of methyl sulfones,[9] we became interested in trifluoroacetylation and other functionalization of alkanesulfonamides and have found that the reaction of the anions of methanesulfonamides with aryl isothiocyanates gave 1,2-dithiole-4-sulfonamides

in one pot.

The reactions of the anion of *N,N*-diisopropylmethanesulfonamide (**1**, R^1=R^2=isopropyl) generated by butyllithium *in situ* at -78 ℃ in THF with carbon disulfide or *N,N'*-dicyclohexylcarbodiimide gave no isolable products. However, its reaction with phenyl isocyanate yielded a 2:1 addition product, propanediamide (**5**), in a good yield. The product (**5**) was always the only isolable product, even if an equimolar amount of **1**, phenyl isocyanate, and butyllithium was used. On the other hand, when the reaction with phenyl isothiocyanate was carried out under similar reaction conditions, a different type of product, 1,2-dithiole, was obtained in 37% yield. The analytical and spectral data were in accord with the structure of *N,N*-diisopropyl-5-anilino-3-phenylimino-1,2-dithiole-4-sulfonamide (**9a**); in the ^{1}H-nmr spectrum, a D_2O-exchangeable proton was observed at an abnormally low field (δ 10.03 ppm),



suggesting that a hydrogen bond exists between the NH and the sulfonyl group. Indeed, in some enaminosulfonamides[10] and enaminosulfones,[11] such a low field shift due to an intramolecular hydrogen bond is known; for example, in the nmr spectrum of (*N*-phenyl)enaminosulfonamide (**8**), the (*E*) form shows the resonance of NH at δ 2.97, while that of the (*Z*) form is detected at δ 8.77.[10] The structure was further confirmed by applying the known ring transformation of 5-anilino-3-phenylimino-1,2-dithiole to 3,5-dianilinopyrazole;[12] a mixture of **9a** and hydrazine hydrate in pyridine was heated at reflux, and the corresponding pyrazole (**10**) was separated in 51% yield after column chromatography.

Table 1. Preparation of Compounds (9a - n)

				Yield	mp	Analysis (%)					
						Calcd			Found		
9	R^1	R^2	Ar	(%)	(℃)	C	H	N	C	H	N
a	i-Pr	i-Pr	Ph	55	218-219	56.34	5.62	9.38	56.36	5.70	9.10
b	i-Pr	i-Pr	4-MeC_6H_4	38	157-158	58.07	6.14	8.83	58.29	6.29	8.84
c	i-Pr	i-Pr	4-ClC_6H_4	41	175-177	48.83	4.48	8.13	48.84	4.58	7.88
d		-$(CH_2)_4$-	Ph	55	223-224	54.65	4.58	10.06	54.57	4.66	10.00
e		-$(CH_2)_4$-	4-MeC_6H_4	35	202-204	56.60	5.20	9.42	56.52	5.29	9.29
f		-$(CH_2)_4$-	4-ClC_6H_4	46	205-207	46.91	3.52	8.63	46.90	3.56	8.33
g		-$(CH_2)_5$-	Ph	50	185-187	55.65	4.90	9.73	55.63	5.04	9.60
h		-$(CH_2)_5$-	4-MeC_6H_4	35	195-197	57.48	5.48	9.14	57.29	5.58	8.97
i		-$(CH_2)_5$-	4-ClC_6H_4	48	233-235	47.99	3.82	8.39	47.82	3.94	8.17
j	H	i-Pr	Ph	25	193-194	53.30	4.72	10.36	53.46	4.85	10.14
k	H	i-Pr	4-MeC_6H_4	7	132-133	55.39	5.34	9.69	55.35	5.21	9.67
l	H	i-Pr	4-ClC_6H_4	10	185-187	45.57	3.61	8.86	45.52	3.61	8.71
m	H	t-Bu	Ph	10	158-160	54.38	5.04	10.01	54.34	5.06	9.93
n	H	t-Bu	4-MeC_6H_4	5	197-200	56.34	5.62	9.38	56.41	5.59	9.27

In spite of the change in the molar ratio of the starting sulfonamide (**1**) (R^1=R^2=isopropyl) to butyllithium from 1:1 to 1:2, the product (**9a**) was the only isolable product. This can be explained by two paths (a) and / or (b) as follows; (a) the initially formed monoanion (**2**) attacks at aryl isothiocyanate to give the monoadduct (**4**), which changes to the carbanion (**7**) by proton exchange. Further attack of **7** at another isothiocyanate would produce dithioamide (**6**). However, an alternative direct path (b) from the dianion (**3**) to (**6**) remains possible, because the formation of the α, α-dicarbanion on the methyl carbon of aryl

methyl sulfone has been reported.[1] Dithioamide (**6**) formed after quenching by acid seems to be oxidized by air during the workup to yield the final product (**9**). In order to improve the yield some oxidizing reagents such as iodine or iron(III) chloride were tested, and the best yield (55%) of **9a** was accomplished by adding hydrogen peroxide to the reaction mixture after the reaction was quenched by acid. Other 1,2-dithiole derivatives (**9a-n**) were prepared in this manner, and the physical and spectral data are summarized in Tables 1 and 2.

The related propanedithioamides corresponding to the intermediates (**6**) have been isolated and oxidized by halogen to give 5-amino-3-imino-1,2-dithiolium salts,[12, 13] which were then neutralized by base to yield free 1,2-dithioles.[12] This process was achieved in one step using halogen in the presence of triethylamine.[14] It is noteworthy that, compared with the above reports,[12-14] our method has the advantage of direct synthesis of 1,2-dithioles in one pot from readily available methanesulfonamides and aryl isothiocyanates without isolation of the intermediary propanedithioamides or 1,2-dithiolium salts.

EXPERIMENTAL

Melting points were determined with a MRK MEL-TEMP II and are uncorrected. Ir spectra were recorded on a JASCO A-102 spectrophotometer. Mass and ^{1}H-nmr spectra were taken with a JEOL JMS DX-300 spectrometer and a JEOL GSX-400 spectrometer, respectively. Microanalyses were performed with a YANAKO CHN-Coder MT-5. The starting methanesulfonamides were prepared from methanesulfonyl chloride and the corresponding amines in the usual manner.[15]

5-Arylamino-3-arylimino-1,2-dithiole-4-sulfonamides (9a-n)

A General Procedure. To a solution of **1** (3.0 mmol) in dry THF (12 ml) 1.5 M solution of n-butyllithium in hexane (4.0 ml, 6.3 mmol) was slowly added at -78 ℃ under a nitrogen atmosphere. The reaction mixture was stirred at -30 ℃ for 30 min. After the temperature was again cooled to -78 ℃, aryl isothiocyanate (6.3 mmol) was added to the reaction mixture, and then the stirring was continued for 24 h at room temperature. After quenching with 12% hydrochloric acid (5 ml), 30% hydrogen peroxide (3.0 ml, 26 mmol) was added to the resulting mixture, and it was stirred for 12 h at room temperature. The crystalline product which separated out (except in the case of **9m**) was collected by filtration. The filtrate was extracted with ether, and the additional crystalline product (in the case of **9a**, **d**, **f**, **i-l**, and **n**) was obtained by concentration of the ethereal extract. In the case of **9b**, **c**, **e**, **g**, **h**, and **m** the extract gave an

Table 2. Spectral Data of Compounds (9a-n)

9	Ms, m/z (%)	Ir (KBr), cm^{-1}	^{1}H-Nmr, δ
a	447 (M^+, 1)	3250, 1605, 1530	1.37 (d, J=6.5 Hz, 12H), 4.06-4.16 (m, 2H), 6.95-7.54
	191 (75), 100 (100)	1300, 1185, 1110	(m, 10H), 10.03 (s, 1H), ($CDCl_3$)
b	475 (M^+, 10)	3180, 1615, 1530	1.35 (d, J=6.5, 12H), 2.32 (s, 3H), 2.37 (s, 3H), 4.05 -
	246 (100), 205 (91)	1290, 1180, 1100	4.15 (m, 2H), 6.86 (m, 8H), 9.87 (s, 1H) ($CDCl_3$)
c	416 (M^+-100, 2)	3200, 1605, 1530	1.35 (d, J=6.9 Hz, 12H), 4.01-4.11 (m, 2H), 6.90-7.41
	225 (26), 100 (100)	1470, 1310, 1100	(m, 8H) ($CDCl_3$)
d	348 (M^+-69, 19)	3240, 1610, 1540	1.94-1.96 (m, 4H), 3.60 (t, J=6.0 Hz, 4H), 6.94-7.44 (m,
	191 (75), 77 (100)	1325, 1305, 1120	10H), 9.96 (s, 1H) ($CDCl_3$)
e	445 (M^+, 7)	3230, 1610, 1530	1.92-1.96 (m, 4H), 2.33 (s, 3H), 2.37 (s, 3H), 3.60 (t,
	279 (93), 247 (100)	1420, 1300, 1110	J=5.2 Hz, 4H), 6.85-7.20 (m, 8H), 9.81 (s, 1H) ($CDCl_3$)
f	408 (M^+-77, 24)	3250, 1555, 1480	1.93-1.95 (m, 4H), 3.57 (t, J=6.4 Hz, 4H), 6.89-7.43 (m,
	225 (100), 111 (86)	1415, 1310, 1130	8H), 9.93 (s, 1H) ($CDCl_3$)
g	431 (M^+, 10)	3250, 1605, 1530,	1.60-1.69 (m, 6H), 3.44 (t, J=5.0 Hz, 4H), 6.96-7.44 (m,
	284 (97), 219 (100)	1405, 1310, 1120	10H), 9.93 (s, 1H) ($CDCl_3$)
h	459 (M^+, 12)	3240, 1580, 1530	1.58-1.67 (m, 6H), 2.33 (s, 3H), 2.37 (s, 3H), 3.43 (t,
	247 (100), 205 (79)	1500, 1415, 1305	J=6.0 Hz, 4H), 6.89-7.20 (m, 8H), 9.78 (s, 1H) ($CDCl_3$)
i	499 (M^+, 3)	3180, 1590, 1535	1.60-1.66 (m, 6H), 3.41 (t, J=5.0 Hz, 4H), 6.91-7.20 (m,
	225 (41), 84 (100)	1480, 1420, 1295	8H), 9.87 (s, 1H) ($CDCl_3$)
j	405 (M^+, 9)	3270, 1600, 1540	1.31 (d, J=6.5 Hz, 6H), 3.57-3.60 (m, 1H), 6.08 (d,
	191 (65), 77 (100)	1320, 1150, 1115	J=5.2 Hz, 1H), 6.99-7.45 (m, 10H), 9.67 (s, 1H) ($CDCl_3$)
k	433 (M^+, 18)	3250, 1600, 1540	1.39 (d, J=6.3 Hz, 6H), 2.33 (s, 3H), 2.38 (s, 3H), 3.52-
	246 (100), 91 (88)	1440, 1310, 1110	3.59 (m, 1H), 6.11 (d, J=5.8 Hz, 1H), 6.89-7.26 (m, 8H),
			9.53 (s, 1H) ($CDCl_3$)
l	473 (M^+, 26)	3300, 1580, 1535	1.16 (d, J=6.6 Hz, 6H), 3.45-3.53 (m, 1H), 6.98 (d,
	225 (97), 111 (100)	1480, 1440, 1320	J=7.7 Hz, 1H), 7.31-7.55 (m, 8H), 9.91 (s, 1H) (DMSO-d_6)
m	419 (M^+, 36),	3270, 1530, 1450	1.43 (s, 9H), 6.30 (s, 1H), 7.01-7.46 (m, 10H), 9.65 (s,
	404 (100), 77 (92)	1385, 1310, 1130	1H) ($CDCl_3$)
n	447 (M^+, 45)	3230, 1520, 1420	1.40 (s, 9H), 2.35 (s, 6H), 6.34 (br s, 1H), 7.07-7.19 (m,
	432 (100), 246 (71)	1310, 1150, 1030	9H) ($CDCl_3$)

oily residue, which was purified by column chromatography on silica gel with an eluent of chloroform to give the product. The yields of the combined products are shown in Table 1. The solvents for recrystallization were AcOEt for **9a**, **c-i**, MeOH for **9j-m**, and $CHCl_3$-hexane for **9b**, **n**.

2-(*N*,*N*-Diisopropylsulfamoyl)-*N*,*N'*-diphenylpropanediamide (5)

Compound (**5**) was prepared in a manner similar to that described above. 97% Yield: mp 193-194 ℃ (MeOH); ir (KBr) 3260, 1690, 1600, 1515, 1440, 1330, 1130 cm^{-1}; ms m/z (%) 417 (M^+, 16), 254 (11), 135 (20), 100 (70), 93 (100); ^{1}H-nmr ($CDCl_3$) δ 1.31 (d, J=6.3 Hz, 12H), 3.78-3.85 (m, 2H), 5.10 (s, 1H), 7.17-7.60 (m, 10H), 9.22 (s, 2H). *Anal.* Calcd for $C_{21}H_{27}N_3O_4S$: C, 60.41; H, 6.51; N, 10.06. Found: C, 60.61; H, 6.51; N, 9.98.

***N*,*N*-Diisopropyl-3,5-dianilinopyrazole-4-sulfonamide (10)**

A mixture of **9a** (447 mg, 1.0 mmol) and 99% hydrazine monohydrate (250 mg, 5.0 mmol) in pyridine (5 ml) was refluxed for 2 h. After cooling, water was added to the mixture, and the mixture was extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give a brown oily residue, which was purified by column chromatography on silica gel with an eluent of chloroform to afford **10** (210 mg, 51% yield) as white powder: mp 109-110 ℃ (cyclohexane); ir (KBr) 3300, 1545, 1495, 1370, 1280, 1180, 1100 cm^{-1}; ms m/z (%) 413 (M^+, 100), 264 (22), 250 (60), 219 (47); ^{1}H-nmr ($CDCl_3$) δ 1.34 (d, J=6.8 Hz, 12H), 3.67 (m, 2H), 7.03 (br s, 2H), 7.26-7.32 (m, 10H). *Anal.* Calcd for $C_{21}H_{27}N_5O_2S$: C, 60.99; H, 6.53; N, 16.94. Found: C, 60.99; H, 6.55; N, 16.73.

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